

CLAIMS: -

1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.
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2. A multiparticulate bisoprolol formulation according to Claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations *in vivo* for a period of at least 3-6 hours.
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3. A multiparticulate bisoprolol formulation according to Claim 1 or 2, which contains a pharmaceutically acceptable salt of bisoprolol.
4. A multiparticulate bisoprolol formulation according to Claim 3, wherein the salt is bisoprolol hemifumarate.
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5. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the following:
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- (a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;
- 5 (b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and
- (c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

10 6. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period

15 substantially corresponds to the following:

- (a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;
- 20 (b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and
- (c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

7. A multiparticulate bisoprolol formulation according to any preceding claim, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.
- 5 8. A multiparticulate bisoprolol formulation according to Claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.
- 10 9. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1mm.
- 15 10. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.
- 20 11. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.
- 25 12. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is a methacrylic acid co-polymer.

13. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is an ammonio methacrylate co-polymer.
- 5 14. A multiparticulate bisoprolol formulation according to Claim 12 or 13, wherein a mixture of said polymers is used.
- 10 15. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.
- 15 16. A multiparticulate bisoprolol formulation according to Claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.
- 20 17. A multiparticulate bisoprolol formulation according to Claim 15 or 16, wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.
18. A multiparticulate bisoprolol formulation according to any one of Claims 15-17, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.
- 25 19. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more

auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to any
5 preceding claim, wherein the coating polymer is coated to 10% to 100%
weight gain on the core.

21. A multiparticulate bisoprolol formulation according to any
preceding claim, wherein the coating polymer is coated to 25% to 70%
10 weight gain on the core.

22. A multiparticulate bisoprolol formulation according to any
preceding claim, wherein a sealant or barrier layer is applied to the
polymeric coating.

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23. A multiparticulate bisoprolol formulation according to Claim 22,
wherein the sealant or barrier is selected from hydroxypropyl
methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose
and xanthan gum.

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24. An oral dosage form containing a multiparticulate bisoprolol
formulation according to any one of Claims 1-23, which is in the form of
caplets, capsules, particles for suspension prior to dosing, sachets or
tablets.

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25. An oral dosage form according to Claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

5 26. A multiparticulate bisoprolol formulation according to Claim 1, substantially as hereinbefore described and exemplified.

27. An oral dosage form according to Claim 24, substantially as hereinbefore described.